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Effects of cyproterone acetate, LHRH agonist and ovarian surgery in McCune-Albright syndrome with precocious puberty and galactorrhea

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ABSTRACT. We have studied the endocrinological pattern in a girl with McCune-Albright syndrome. The young patient showed: normal prepubertal serum levels of gonadotropins, fluctuating estrogen concentrations, which sometimes were similar to the levels in adult women of fertile age, hyperprolactinemia with galactorrhea, ovarian cysts. The effects of treatment with antiandrogen drug, cyproterone acetate, and of a LHRH agonist, buserelin (<D-Ser[TBU^{8}6-des-gly NH2.10 > LHRH ethylamide), were studied. Cyproterone acetate with or without buserelin did not fully suppress estradiol concentrations. On the other hand, surgical resection of these cysts resulted in both clinical and endocrinological remission. It is likely that in this case of McCune-Albright syndrome precocious puberty was a result of ovarian estrogen secretion, while pubertal activation of the hypothalamus-pituitary axis was absent. Hyperprolactinemia, which appeared after the beginning of the combined therapy with buserelin and cyproterone acetate, was probably due to the elevated estrogen levels.

INTRODUCTION

The McCune-Albright syndrome, described in the 1930s (1, 2), but first mentioned by Weil in 1922 (3), is defined by a triad characterized by precocious puberty, polyostotic fibrous dysplasia and "café au lait" skin pigmentation. Variant forms of the classic syndrome with only two out of the three findings have been recognized (4). Furthermore, other endocrine disorders may be present in patients with McCune-Albright syndrome, such as Cushing's syndrome (5), acromegaly (6, 7), hyperthyroidism (8) and hyperparathyroidism (9).

The mechanism of the onset of precocious puberty in girls with McCune-Albright syndrome is still debated (10-18). Benedict in 1966 first suggested that precocious puberty might be caused by premature activation of the hypothalamus-pituitary-gonadal axis at a high level (true precociuos puberty) (4); usually this type of puberty is idiopathic (15, 16), but may also be sustained by pituitary adenoma (17, 18). Recently, Foster et al. (19) postulated that autonomous hyperfunction of the ovary, producing estrogen in excess, might be the cause of the syndrome and that no alteration in gonadotropin release, which remains in the prepubertal range, can be detected. We report here a case which support the latter hypothesis.

Key-words: McCune-Albright syndrome, precocious puberty, glactorrhea, hyperprolactinemia, cyproterone acetate, LHRH agonist.

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CASE REPORT

At the time of the report the patient was a 4 year and 3 months old girl, who first came to our attention when she was one year-old because of vaginal bleeding. Since she was four months old, her mother had noted a white, blood-streaked mucoid discharge in her diaper. The vaginal bleeding recurred nearly every month with profuse flow.

When the girl was first referred to our Department, she showed II-III stage breasts and II stage pubic hair, according to Tanner (14). The child's height was 88 cm (90th percentile). She also had "café au lait" skin pigmentation extending from her neck to the right shoulder and from the lumbar region to the buttocks. At the time a pathological bone fracture had just occurred: radiological investigation revealed areas of fibrous bone dysplasia. Several other bone fractures occurred during the following yr.

The following assays, each of which was the average of three evaluations carried out at 15-min intervals, were repeated several time approximately ever 14 days. Levels of serum LH, FSH, PRL, estradiol, T_3, T_4, TSH, and cortisol and of urinary free cortisol were estimated by conventional double antibody radioimmunoassay; international reference preparations of FSH (MRC 78/549) and LH (MRC 68/40) were used to standardize assays of serum gonadotropins. The inter- and intraassay coefficients of variation for each assays were below 10%. The average of each hormonal evaluations are shown as bars in Figure 1.

Gonadotropin and prolactin levels, at the first evaluation, were within the normal ranges for age (LH =

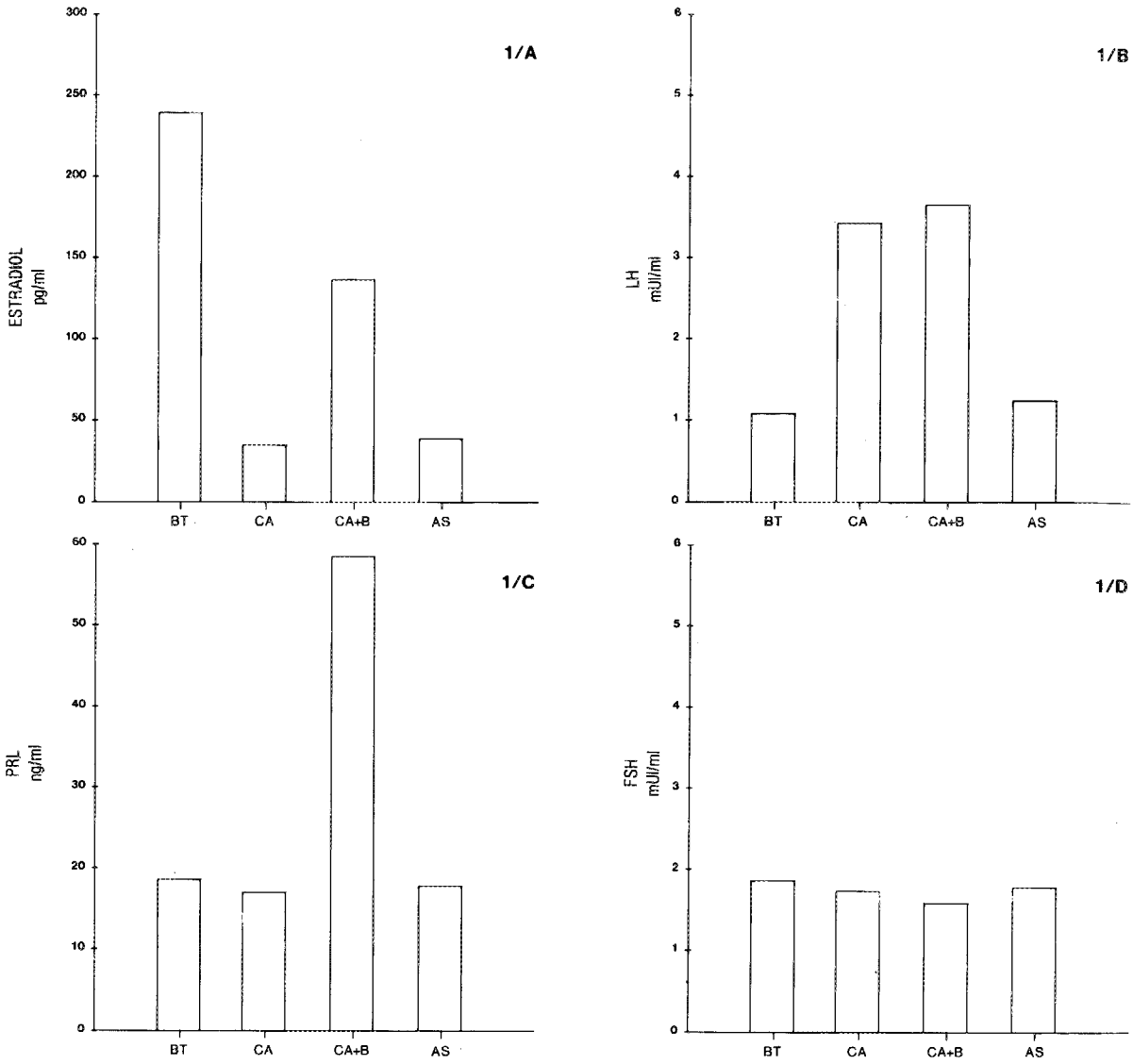

Fig. 1 - *Average serum levels of estradiol, PRL, LH and FSH in the girl with McCune-Albright syndrome before treatment (BT), on cyproterone acetate (50 mg) treatment (CA), on cyproterone acetate (25 mg) plus buserelin (1.2 mg) treatment (Ca +B) and after surgery (AS).*

1.8-2.3-1.0-3.7 mUI/ml; FSH = 1.5-2.4-2.0-1.8 mUI/ml; normal range for age: < 5.0 mUI/ml for both the hormones. PRL = 18.2-19.8-17.5-10.6 ng/ml; normal values: 5-20 ng/ml), whereas serum levels of estradiol increased to 147-323-94.7-526 pg/ml (normal values for age: < 20 pg/ml). Thyroid (T_3, T_4 and TSH serum levels) and adrenal (morning-evening levels of serum cortisol and urinary free cortisol) function was normal. Pelvic echographic study was carried out. Small anatomostructural anomalies could not be detected because of the restlessness of the little girl, however the echographic study (which was repeated twice) showed that there were no sizeable cysts and that the volume of the ovaries (less than 1 cm diameter) was not abnormal for the age.

Computerized tomography of the head, performed after general anesthesia with contrast medium, showed no abnormalities of the hypothalamus-pituitary axis, but detected some areas of fibrous dysplasia at the base of the skull.

The diagnosis of McCune-Albright syndrome was made and cyproterone acetate (Androcur®, Shering), 50 mg/daily, was administred orally.

Hormone deteminations during therapy with cyproterone acetate showed: prepubertal levels of gonadotropins (LH = 5.0-2.0-1.6 - mUI/ml; FSH = 1.9-1.5-2.0

mUI/ml); rising and falling estradiol levels (25.0-97.0-15.6 pg/ml) which were below pretreatment levels; normal serum basal levels of PRL (14.3-25.0-18.7 ng/ml): only one of the three values was at the upper limit of the normal range, corresponding to the peak estradiol level; normal serum cortisol levels: 13.0-16.6-10.5 ng/100 ml (normal range: 5-25 ng/100 ml) and urinary free cortisol levels: 78-83-72 μg/24 h (normal range: 70-320 mcg/24 hours).

Despite this therapy, menses persisted at a variable rate, intensity and period. When she was 3-yr-old, the height was at the 97th percentile (102 cm) and bone age was 6 yr.

During the following 2 yr her clinical condition progressively improved as did the endocrine pattern. For example, at the age of 3 yr and 9 months the patient showed: LH = 5.0 mUI/ml, FSH = 1.4 mUI/ml, estradiol = 30 pg/ml; even though vaginal bleeding persisted, episodes were rarer (every 3-4 months) and, at the same time, the pubertal state did not develop further (II-III stage breasts and II stage pubic hair).

Four months later the child was admitted to our Department because of the onset of bilateral galactorrhea. She showed III stage breasts, which were particularly turgid with spontaneous leakage of milk; pubic hair was at the second stage.

Endocrinological investigation again showed prepubertal levels of gonadotropins (LH = 5.0-3.7-1.8-4.2 mUI/ml; FSH = 1.5-2.0-1.3-1.9 mUI/ml), whereas estrogens and prolactin exceeded normal range (estradiol = 236-192-106-10 pg/ml; PRL = 32-66-86-48 ng/ml). The pelvic echographic study revealed a large pelvic central cyst, which displaced the bladder and uterus from their normal location and a second cyst in the right ovary; the uterus was also large for patient's age. Computerized tomography of abdominal and pelvic regions confirmed the ultrasound findings. Computerized tomography of the brain showed no abnormalities.

The patient underwent surgical resection of the cysts: histological study of the section revealed that the larger one was a parametrial cyst, whereas cystic antral follicles were found in the right ovary. Sex steroid content of the ovarian cyst showed high estradiol levels (in antral fluid: estradiol = 4214 ng/ml, progesterone = 131 ng/ml, androstenedione = 518 ng/ml) whereas very low hormone concentrations were detected in the parametrial cyst (estradiol < 15 pg/ml, progesterone and androstenedione < 1 ng/ml) suggesting that estrogens were produced by the ovary. After surgical resection, both menses and galactorrhea stopped. Furthermore, estradiol and prolactin levels returned to the normal range.

After five months, clinical and endocrinological features still indicated remission of the syndrome (LH = 2.4-4.2-3.1-5.0 mUI/ml; FSH = 1.8-2.3-1.4-2.0 mUI:ml; estradiol = 75.0-34.7-18.4-31.4 pg/ml; PRL = 27.5-19.0-15.2-13.0 ng/ml) (Fig. 1).

COMMENT

Many references support the central hypothalamic origin of precocious puberty in the McCune-Albright syndrome (1, 10). On the other hand, in 1951 Pray et al. described clinical and endocrinological remission of the syndrome after excision of an ovarian cyst in a 4 yr-old girl (21). D'Armiento and Danon reported two cases of McCune-Albright syndrome with low gonadotropin levels (5, 22). More recently, in 1984 Foster et al. described 5 cases of McCune-Albright syndrome with precocious puberty and high serum levels of estradiol, low gonadotropin concentrations together with ovarian cysts (19).

In the present report, the McCune-Albright syndrome is described in a 4-yr-old girl, who showed serum gonadotropin within prepubertal levels, marked fluctuations of estrogen, varying levels of prolactin and was treated, at different times, with an antiandrogen compound, cyproterone acetate, with a LHRH agonist, buserelin, and with surgical treatment of the ovary.

Daily administration of an antiandrogen drug having also progestational and antiagonadotropic activity, cyproterone acetate, did not improve the clinical pattern of the patient, even though estrogen concentrations were low during the treatment period. We suggest that the administration of cyproterone acetate lowered these concentrations, but cannot demonstrate this since in children with McCune-Albright syndrome the disorder is characterized by periods of spontaneous remission and wide fluctuation of estradiol levels. Stanhope et al. in 1985 (23) suggested that the predominant effect of cyproterone acetate, in addition to its peripheral action, is a direct inhibition of ovarian steroidogenesis, as demonstrated *in vitro* by Schurenkamper and Lisse in 1982 (24).

The long-acting LHRH agonist, buserelin, which was secondarily associated with cyproterone acetate, has been shown not only to act at the pituitary level, but also to inhibit gonadal steroidogenesis in *in vitro* models (25, 26). A similar mechanism has been previously postulated also in humans (27), but more recently other authors have demonstrated that inhibition exerted by buserelin is not sufficient to suppress ovarian estrogen secretion (18-30). Rather, it lowers serum estrogen levels in human beings by inhibiting pituitary gonadotropin release (31). This could explain the failure of our therapy with LHRH analogue. Combined administration of buserelin and cyproterone acetate (25 mg daily) was accompanied by a worsening of the clinical and endocrinological pattern. During the treatment with buserelin and cyproterone acetate, we observed a rise in serum estradiol and prolactin levels (Fig. 1). At the same time menses persisted and turgid development

of the breasts with galactorrhea occurred. Both endocrinological and clinical aspects could be a consequence of the treatment.

Finally, it is very significant that after surgery, i.e. ovariectomy, both serum estrogen and prolactin levels fell and vaginal bleeding plus galactorrhea disappeared.

As for the pathogenesis of McCune-Albright in our young patient, we suggest that the clinical picture originated from episodic estradiol hypersecretion, which caused in particular the precocious appearance of sexual secondary characters, vaginal bleeding, postmenarchal size and shape, growth and bone age significantly inappropriate for age and also hyperprolactinemia and galactorrhea. Several authors postulated that elevated sex steroid concentration during precocious puberty may cause early maturation of the hypothalamus-pituitary axis and rise gonadotropin levels (19). Thus it is conceivable that both the "central" and the "peripheral" hypothesis of the pathogenesis of precocious puberty in McCune-Albright syndrome, may be sustained by anatomous activation. Some new knowledge has been gained about the pathogenesis of McCune-Albright syndrome, but it is very difficult to come to any conclusion concerning the etiology of this disorder. Giovannelli et al., (32) hypothesize that the presence in ovary of embryonic cell clones having aberrant response to otherwise normal stimuli, but further studies are needed before this theory can be fully assessed.

We would underline hyperprolactinemia in the case of McCune-Albright syndrome, which is a peculiarity, because it has been rarely described (7, 18, 33). It is well recognized that elevated estrogen levels per se lead to a stimulation of estrogen secretion by means of a direct action at the pituitary level, by increasing the number of receptor sites of TRH and probably through a potent antiandrogen activity (34). So, we suggest that elevated estrogen levels may have played a role in the pathogenesis of hyperprolactinemia in our patient.

In conclusion, this case is noteworthy first of all because it corroborates the thesis of an ovarian precocious puberty in McCune-Albright syndrome, with episodic estradiol secretion, following cyclic ovarian cyst formation. Secondly, it revealed hyperprolactinemia which, together with high levels of estrogens, caused marked galactorrhea. Thirdly, we observed that treatment for 4 months with LHRH agonist failed to ameliorate ovarian precocious puberty. In agreement with Comite et al. (35), this suggests that the syndrome was not gonadotropin-dependent, even though it is not possible to reach definite conclusions because of the shortness of the period of treatment with buserelin.

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